Article

Efficacy and safety of 3 versus 5 days of meloxicam as an analgesic for feline onychectomy and sterilization

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Abstract — Three- or 5-day courses of meloxicam [0.2 mg/kg body weight (BW) subcutaneously pre- or post-operatively on Day 1 followed by 0.05 mg/kg BW, PO per day thereafter] were assessed for analgesic efficacy and safety in 50 client-owned cats undergoing onychectomy and sterilization. Primary outcome parameters were analgesia score, gait/lameness score, and need for rescue analgesia assessed at times 0, 1, 4, 7, 24, 28, 35, 48, 52, 57 hours and on Day 5. Packed cell volume/total solids and serum biochemistry were assessed at time 0 and Days 3 and 5. There were no differences in efficacy and safety parameters regardless of the treatment protocol employed and no cat required rescue analgesia. The patients that received meloxicam preoperatively had statistically better gait/lameness scores than those that received meloxicam postoperatively, supporting the principle of preemptive analgesia.

Résumé — Efficacité et innocuité de 3 versus 5 jours de méloxicam comme analgésique pour l'onychectomie et la stérilisation félines. Des traitements d'une durée de 3 ou 5 jours au méloxicam (0,2 mg/kg par administration sous-cutanée avant ou après l'opération le jour 1, suivi de 0,05 mg/kg poids corporel (PC), PO par jour ensuite) ont été évalués pour l'efficacité et l'innocuité analgésiques chez 50 chats, qui appartenaient à des clients, subissant l'onychectomie et la stérilisation. Les paramètres primaires des résultats étaient la cotation analgésique, la cotation de la démarche et de la boiterie et le besoin d'analgésie de secours évalué aux moments 0, 1, 4, 7, 24, 28, 35, 48, 52, 57 heures et le jour 5; le ratio valeur d'hématocrite/total des solides et les résultats de la biochimie sérique ont été examinés aux moments 0 et aux jours 3 et 5. Il n'y avait aucune différence au niveau des paramètres d'efficacité et d'innocuité sans égard au protocole de traitement employé et aucun chat n'a exigé une analgésie de secours. Les patients qui recevaient le méloxicam avant l'opération présentaient statistiquement de meilleurs pointages de démarche et de boiterie que ceux qui avaient reçu le méloxicam après l'opération, ce qui appuie le principe d'une analgésie préventive.

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Introduction

Pain during surgical procedures is a well-accepted physiological occurrence in animals. However, its treatment is hampered by the ability to adequately recognize signs of pain in dogs and cats, which has led to a philosophical shift in small animal pain management signified by the adage "treat predictable pain," especially when no contraindications to pain treatment exist. Despite these attitudinal shifts in veterinary teaching and the profession at large, actual treatment fails to meet predicted pain incidence. In a review of perioperative use of analgesics by Canadian veterinarians, the authors of 1 study estimated that there were still 6000 dogs and cats undergoing ovariohysterectomy on a monthly basis that were not receiving appropriate pain management (1). While this is likely partially due to different levels of pain management education and attitude between various generations of veterinarians, it is also fuelled by lingering questions over the efficacy and safety of various analgesics, especially when used during the higher-risk period of anesthesia and surgery.

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Opioids remain the mainstay of treating acute pain, but they carry individual and class-specific limitations, including variable analgesic efficacy and short duration of action. Nonsteroidal antiinflammatory drugs (NSAIDs) have become increasingly popular for their dual analgesic and antiinflammatory effects, once-per-day dosing, easy scripting, and pet owner compliance. However, issues related to safety remain an impediment to broader use, especially in the feline species, which have been cited as being more prone to the renal effects of NSAIDs. This concern is compounded by the potential hypotensive perioperative period, and a species-specific reduced ability to metabolize drugs through hepatic glucuronidation (2–6).

Meloxicam is an enolic NSAID of the oxicam class; its pharmacological profile in the cat has been the subject of several pharmacological and clinical reviews (3–9). It is a unique molecule in that it is metabolized through oxidative rather than glucuronidation pathways, which has recently been confirmed in the cat (10). This results in a consistent and predictable metabolic profile that, in conjunction with meloxicam's 24 h half-life and COX-1 sparing profile in the cat, makes meloxicam ideal for repetitive use (11–14). Meloxicam's efficacy and safety have also been extensively studied in cats, both through the regulatory requirements inherent in licensing meloxicam as a veterinary pharmaceutical, and in the published literature assessing perioperative and chronic use efficacy and renal/gastrointestinal safety (15–26). Meloxicam has also been recommended as part of preventative and/or therapeutic protocols for "chronic pain syndrome," which has been associated with feline onychectomy and theorized to be a manifestation of neuropathic pain (27). While the published data have resulted in a chronic-use claim in the EU and Australia (28,29), meloxicam is still licensed in most countries as a single-dose injection for the perioperative period in cats and the published literature has been, for the most part, restricted to the immediate 24-hour post-operative period. However, proper pain management usually involves 3 to 5 days of postoperative analgesic support and anecdotal reports have recommended protocols using meloxicam in this fashion (3,4,6–9).

The purpose of this study was to examine the safety and efficacy of 2- versus 4-day use of meloxicam following an initial parenteral dose for the management of pain associated with onychectomy and ovariohysterectomy/orchidectomy in cats.

Materials and methods

Animals and treatments

Cats older than 16 wk undergoing onychectomy with sterilization (ovariohysterectomy or orchidectomy) were recruited from the regular patient population of 3 participating small animal veterinary hospitals. Participation was based on the receipt of owner-informed consent and animals were randomized to receive meloxicam oral suspension for either 2 or 4 days postoperatively following an initial parenteral dose.

All animals underwent a similar preoperative assessment of a general physical examination and a packed cell volume (PCV), total solids (TS), and a serum biochemical assessment comprised of determination of glucose, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), and alkaline phoshpatase (ALP). Only those animals found to be free of any comorbid illnesses were acceptable for study enrollment. Additional exclusionary criteria included pregnancy, administration of an NSAID or NSAID-containing neutraceutical within the previous 14 d, or the administration of a glycosaminoglycan product during the previous 30 d.

All animals received a multi-modal anesthetic induction protocol comprised of intravenous fluid therapy [balanced electrolyte solution administered at surgical fluid rates (10 mL/kg body weight (BW) per hour) during anesthesia]. Premedication was with acepromazine (Atravet 10 mg/mL; Ayerst Veterinary Laboratories, Guelph, Ontario), 0.05 mg/kg BW, intramuscularly (IM); glycopyrrolate (Glycopyrrolate 0.2 mg/mL; Sandoz, Boucherville, Quebec), 0.011 mg/kg BW, IM; hydromorphone (Hydromorphone 2 mg/mL; Sandoz), 0.05 mg/kg, IM; and meloxicam (Metacam 0.5% Injection; Boehringer Ingelheim Canada, Burlington, Ontario), 0.2 mg/kg BW, subcutaneously (SC) 30 min prior to induction (although a protocol breech at 1 practice resulted in post-operative administration; see Results section). Induction was with 0.1 mg/kg of a 50:50 mixture of ketamine (Vetalar 100 mg/mL; Bioniche Animal Health, Belleville, Ontario) and valium (Diazepam 5 mg/mL, Sandoz) intravenously (IV). Maintenance anesthesia consisted of isoflurane (Aerrane; Baxter, Mississauga, Ontario) and oxygen; and a ring block employing lidocaine (Xylocaine 2%, AstraZeneca Canada, Mississauga, Ontario) using a published technique (30) for both forepaws immediately after induction. The sterilization procedure was performed first, followed by the onychectomy. Surgical methodology was left to the veterinary surgeon and based on acceptable surgical technique. All onychectomies were performed by the same surgeon within each animal hospital using the surgical blade technique followed by forepaw bandaging that was left in place for 24 h. Perioperative monitoring included temperature, heart and respiratory rate, blood pressure, and pulse oximetry.

Cats assigned to Group 1 received meloxicam test article (meloxicam 0.5 mg/mL oral suspension; Boehringer Ingelheim Canada) at 0.05 mg/kg BW per day, per os (PO) for 4 consecutive days beginning on Day 2 for a total of 5 days of meloxicam treatment. Cats assigned to Group 2 received the meloxicam test article at the same dose but for an additional 2 days PO for a total of 3 days of meloxicam treatment.

Experimental design

The experiment was a randomized, positive controlled, single-blinded (veterinarian) study. Animals were randomized in an alternating assignment to either Group 1 or Group 2 based on an initial coin toss. Blinding was maintained through the use of a clinic-specific case monitor who was responsible for dispensing medication and/or administration but was not involved in patient assessment.

Outcome measures

The study was designed to assess both the efficacy and safety of meloxicam use in the cases treated.

Efficacy. Primary outcome measure for efficacy included analgesia score (AS; Appendix I), gait/lameness score (G/L; Appendix II), and the need for rescue analgesia. Rescue analgesia was defined as necessary if the AS score was 4 or greater and/or

Table 1. Schedule of primary and secondary outcome parameter assessments over time

Time	Procedures
Extubation (T = 0)	
1 h (T + 1)	AS, G/L
4 h (T + 4)	AS, G/L
7 h (T + 7)	AS, G/L
Day 2: 8 am	GPE, weight, AS, G/L Determination of surgical site swelling or discharge Administration of oral test article[a] Removal of bandages
Day 2: noon	AS, G/L
Day 2: 7 pm	AS, G/L
Day 3: 8 am	GPE, weight, AS, G/L Determination of surgical site swelling or discharge Blood taken for PCV/TS, serum chemistry Administration of oral test product[a]
Day 3: noon	AS, G/L
Day 3: 5 pm (if applicable)	AS, G/L
Day 3: pm	Discharged to home (if owner chooses)
Day 4: am	Administration of oral test product by pet owner or clinic monitor (if randomized to group 1)[a]
Day 5: am	Administration of oral test product by pet owner or clinic monitor (if randomized to group 1)[a]
Day 5: pm	GPE, weight, AS, G/L Determination of surgical site swelling or discharge Blood taken for PCV/TS, serum biochemistry

[a] If no signs of illness.
GPE — physical examination, PCV — packed cell volume, TS — total solids, AS — analgesia score, G/L — gait/lameness score.

the G/L was 4 or greater. Choice of rescue analgesia was left to the discretion of the participating veterinarian. Secondary outcome measures included weight, surgical site swelling/discharge, and gastrointestinal upset. All assessments were done by the same veterinarian attending to each case.

Safety. Primary outcome parameters for safety included clinical pathology, as defined above. Samples were collected prior to enrollment and on Days 3 and 5. Pre-enrollment samples were used to assess for study inclusion suitability. All serum biochemistry samples were separated, stored in a refrigerator, and run at the same time upon completion of the study at an established veterinary clinical pathology laboratory (Antech Diagnostics, Mississauga, Ontario).

The schedule for assessment of primary and secondary outcome parameters is given in Table 1.

Statistical analysis

The potential difference between the treatment groups for each measured outcome was examined with a linear model which included treatment group, time, whether or not meloxicam test article was used prior to surgery, the type of surgery and interactions between treatment group and time, as well as between surgery type and time. Repeated measures on individual subjects were accounted for using generalized estimating equations with an autoregressive (AR1) correlation matrix (SPSS Statistics ver. 17.0, SPSS, Chicago, Illinois, USA). The post hoc differences between the means of the treatment groups for the relevant time points were calculated using a least significant difference adjustment for multiple comparisons. Within group comparisons across time were examined with a paired-samples *t*-test comparing day 5 parameters to the baseline parameters collected on day 1 (SPSS Statistics ver. 17.0, SPSS).

Table 2. Summary of baseline parameters compared by group. Summary of study parameters, including physiological, laboratory, and primary study variables, prior to study initiation for cats receiving 4 (Group 1) versus 2 (Group 2) days of post-operative meloxicam

	Group 1	Group 2	
Mean values by group	Day 1 Pre-surgery	Day 1 Pre-surgery	*P*-value
Temperature (°C)	38.82	38.88	0.591
Body weight (kg)	3.84	3.92	0.822
Heart rate (beats/min)	179.25	181.20	0.819
Respiratory rate (breaths/min)	46.96	47.21	0.95
PCV — packed cell volume	41.42	38.40	0.073
Total solids	insufficient data	insufficient data	
BUN — blood urea nitrogen (mmol/L)	8.01	7.88	0.809
Serum glucose (mmol/L)	4.42	4.12	0.4
Creatinine (μmol/L)	99.92	103.84	0.572
ALT (U/L)	61.50	68.60	0.501
Alkaline phosphatase (U/L)	75.58	73.88	0.887
Total protein (g/L)	70.92	69.80	0.492
Analgesia score (1 to 5)	1.00	1.00	NA
Gait/lameness score (1 to 5)	1.00	1.00	NA

NA — not applicable.

Results

Animals

A total of 52 animals from 3 clinics were enrolled in the study. Two cats were removed from the study (1 due to incomplete surgical information and the other due to aggression making post-operative oral treatment impossible) leaving a total of 50 cats (n = 39, 8, and 3, from the 3 clinics) for analysis with 25 cats in each of Groups 1 and 2. No significant differences existed between the groups at the time of study enrollment (Table 2).

Despite the protocol, most cats (n = 32) received their first dose of meloxicam after surgery and not before as outlined. However, the distribution of initial treatment times was identical between the groups, with 9 cats receiving meloxicam before surgery and 16 after surgery.

Efficacy

There were no significant differences between groups with regards to the primary or secondary efficacy parameters at any of the assessment times (Table 3). Both the AS and G/L scores increased on Day 2 and then steadily decreased over time until the last measurement on Day 5. Mean AS for both treatment groups remained less than 2 while the mean G/L scores were between 2 (barely noticeable) and 3 (noticeable but

Table 3. Summary of analgesia and gait/lameness scores compared by group. Mean analgesia and gait/lameness scores over time for cats receiving 4 (Group 1) versus 2 (Group 2) days of post-operative meloxicam, including standard deviation and levels of significance

	Group 1		Group 2		
Mean scores by group	Analgesia	$S_{\bar{x}}$	Analgesia	$S_{\bar{x}}$	*P*-value
Day 1 Pre-surgery	1.00	NA	1.00	NA	NA
Day 1 Extubation plus 1 h	1.04	0.20	1.20	0.40	> 0.05
Day 1 Extubation plus 4 h	1.12	0.33	1.20	0.41	> 0.05
Day 1 Extubation plus 7 h	1.88	0.53	1.84	0.47	> 0.05
Day 2 — 8 am	1.80	0.58	1.88	0.44	> 0.05
Day 2 — 12 pm	1.60	0.50	1.64	0.49	> 0.05
Day 2 — 7 pm	1.24	0.43	1.32	0.48	> 0.05
Day 3 — 8 am	1.08	0.28	1.20	0.41	> 0.05
Day 3 — 12 pm	1.08	0.28	1.16	0.37	> 0.05
Day 3 — 5 pm	1.00	0.00	1.10	0.30	> 0.05
Day 5	1.12	0.33	1.04	0.20	> 0.05
	Gait/ lameness		Gait/ lameness		*P*-value
Day 1 Pre-surgery	1.00	NA	1.00	NA	NA
Day 1 Extubation plus 1 h	1.20	0.45	1.33	0.56	> 0.05
Day 1 Extubation plus 4 h	1.67	0.82	2.00	0.76	> 0.05
Day 1 Extubation plus 7 h	2.40	0.84	2.46	0.78	> 0.05
Day 2 — 8 am	2.58	0.58	2.52	0.71	> 0.05
Day 2 — 12 pm	2.17	0.70	2.24	0.66	> 0.05
Day 2 — 7 pm	2.00	0.59	2.24	0.66	> 0.05
Day 3 — 8 am	1.96	0.54	1.92	0.64	> 0.05
Day 3 — 12 pm	1.92	0.57	1.96	0.67	> 0.05
Day 3 — 5 pm	1.82	0.50	2.00	0.55	> 0.05
Day 5	1.80	0.50	1.76	0.60	> 0.05

$S_{\bar{x}}$ — Standard deviation of the mean.
NA — not applicable.

weight-bearing). Both groups followed a similar pattern for both parameters (Figures 1, 2).

To identify any potential benefit in efficacy or safety from preoperative or postoperative administration of meloxicam, 2 groups (from the combined Groups 1 and 2) were formed: cats that received meloxicam prior to surgery (pre-emptively) and those that received it after surgery (at extubation) with efficacy results depicted in Figures 4 and 5. The cats in the group that received meloxicam at extubation had significantly higher G/L scores the day after surgery and, while they showed a decline over time, they had a higher overall G/L score for the duration of the study compared with the preemptive treatment group; these differences were highly significant at all time points from 4 h post-surgery through to day 5 (*P*-values from 0.001 to 0.049).

No cat required rescue analgesia; however, 1 cat required administration of an opioid for restraint to facilitate reapplication of its bandage.

Safety

No clinically significant differences were observed between treatment groups for the serum biochemistry parameters evaluated — both between Groups 1 and 2 at Days 1, 3, and 5 as well as within Groups between Days 5 and 1. Similar results were obtained when the cats were divided into pre-emptive versus extubation treatment times.

There were differences within Groups 1 and 2 when Day 5 values were compared to Day 1 values (Table 4). While there were some fluctuations in blood parameters within individual animals, they always remained within the laboratory's established reference ranges with only 1 cat demonstrating a greater than 1.5× deviation over time [creatinine at Days 1, 3, and 5 were 51, 47, and 81, respectively (reference range = 79 to 133 μmol/L); blood urea nitrogen (BUN) values were 8.1, 6.4, and 8.1, respectively (reference range = 5.0 to 13.9 mmol/L)].

No gastrointestinal upset was noted, and all cats readily accepted meloxicam administration.

Discussion

This study supports the findings of earlier research demonstrating the efficacy and safety of meloxicam as an analgesic agent for pain management in the cat during the immediate perioperative period. This study is unique and builds upon earlier published data by showing that these findings extend out into the 5-day postoperative period and that preemptive use of meloxicam was associated with better pain management outcomes than was postoperative administration.

Other than label indications, one of the main deterrents to multiple-day use of meloxicam in the peri/postoperative period has been concern over safety — principally with regards to impact on renal function. This has been the subject of much debate and investigation in both the dog and cat, with some theorizing that feline renal physiology may be more prostaglandin dependent (4,26,31). This has been challenged by more recent experimental and retrospective clinical studies that failed to demonstrate impairment in renal function when meloxicam was given, even in the face of pre-existing renal disease (21,25,26). Additionally, several studies have directly evaluated

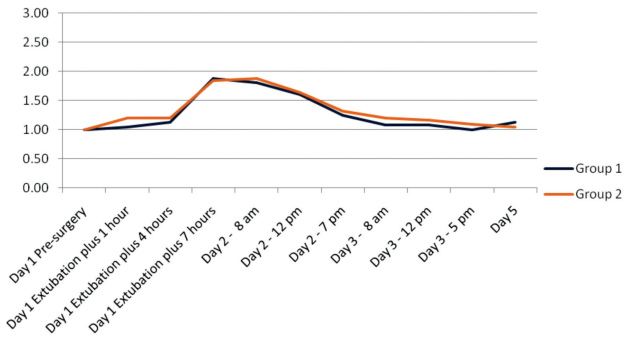

Figure 1. Analgesia scores by group from Day 1 to Day 5. Mean analgesia scores over time for cats receiving 4 (Group 1) versus 2 (Group 2) days of post-operative meloxicam. There is no significant difference between groups.

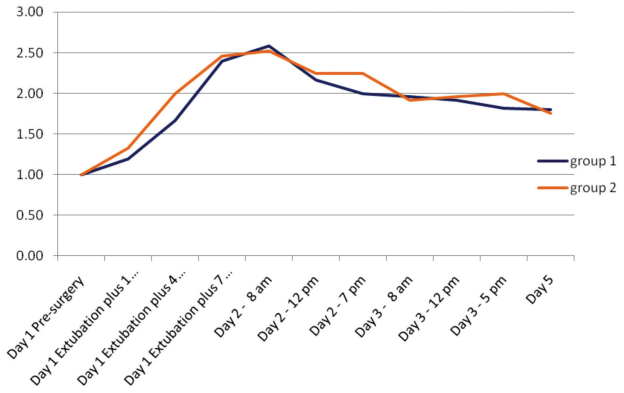

Figure 2. Gait/lameness scores by group from Day 1 to Day 5. Mean gait/lameness scores over time for cats receiving 4 (Group 1) versus 2 (Group 2) days of post-operative meloxicam. There is no significant difference between groups.

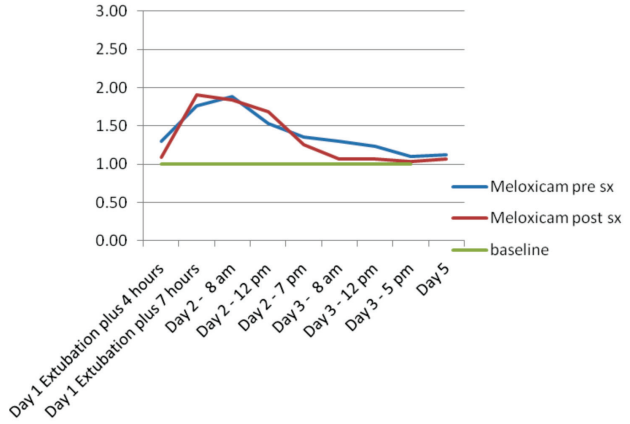

Figure 3. Analgesia scores based on preemptive or postoperative administration of meloxicam. Mean analgesia scores over time for cats receiving meloxicam preemptively (pre sx) or at the time of extubation (post sx). There is no significant difference between groups.

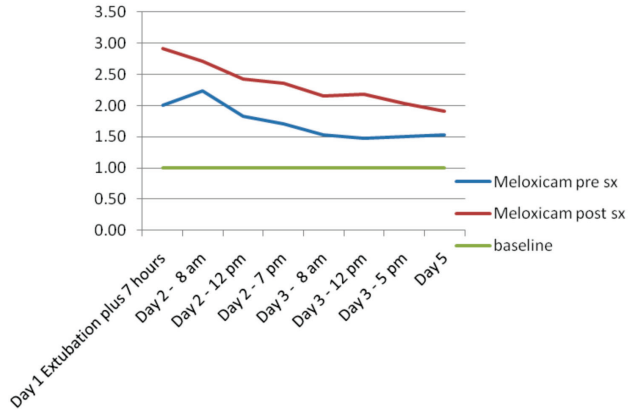

Figure 4. Gait/lameness scores based on premeptive or postoperative administration of meloxicam. Mean gait/lameness scores over time for cats receiving meloxicam preemptively (pre sx) or at the time of extubation (post sx). A significant difference between groups was defined from 4 hours post-surgery to Day 5 (*P*-values from 0.001 to 0.049).

meloxicam's impact on both the conscious and anesthetized dog with no evidence of renal impairment (32–34). A recent study in conscious healthy cats mirror these findings, as does the toxicological data generated as part of the licensing requirements in the European Union (EU) (26,28). When used alone in healthy animals at label doses (based on lean body weight), meloxicam does not have a clinically relevant, negative impact on renal function. This was further supported by the results of this study, which demonstrated no changes in hepatic and renal function on serial serum biochemistry assessment over the 5-day study period. These are similar to findings from other studies that assessed renal function in the perioperative period following meloxicam use (15,17).

Earlier authors had postulated that suspect NSAID-mediated renal adverse events in the perioperative period may be primarily or partially a result of inadequate patient supportive care, including the lack of proper monitoring or IV fluid support (2–4,9). Hypotension plays a significant, if not primary, role in the incidence of postoperative NSAID-associated acute renal failure, and this has been cited as a stand-alone risk factor and can be mitigated by proper perioperative supportive care (including IV fluid support, blood pressure monitoring, and anesthetic dosing to effect) as was employed in this study (35,36). These supportive procedures have now become the foundation for standards governing the perioperative care of the anesthetized veterinary patient (37,38). However, it is still prudent to discuss clinical signs that may be indicative of a postoperative health concern with the pet owners to ensure that they stop any NSAID therapy and seek veterinary advice at their earliest convenience.

This study is the second published that demonstrates the efficacy of a meloxicam 0.5 mg/mL oral suspension when used at 0.05 mg/kg BW, per day for acute perioperative pain (20). A number of anecdotal peri/postoperative treatment protocols using meloxicam have been recommended and these have created some confusion as to what properly balances efficacy with safety. The dose-finding work done for the 0.05 mg/kg BW per day chronic label dose in the EU was based on an acute, experimental, chemically induced synovitis model and its efficacy was confirmed (14). This mirrors earlier

Table 4. Mean and standard deviation of blood parameters assessed on Days 1, 3, and 5 from Group 1, Group 2, meloxicam given prior to surgery (Group PreSx), and meloxicam given at the time of extubation (Group ExTub)

	Day 1		Day 3		Day 5	
Group/value	Mean	*s*	Mean	*s*	Mean	*s*
Group 1						
PCV	41.4	6.1	37.7[a]	5.2	36.5[a]	4.8
TP	70.9	4.4	71.0	5.0	73.2	6.2
BUN	8.0	2.0	6.4[a]	1.7	7.3[a]	2.3
Creatinine	99.9	26.4	79.9[a]	24.2	92.1[a]	23.6
ALT	61.5	18.6	58.6	19.9	55.4	25.5
SAP	75.6	38.6	53.9[a]	26.1	47.8[a]	23.3
Group 2						
PCV	38.4	5.6	36.7	4.9	35.6	5.3
TP	69.8	6.7	70.0	5.9	71.2	7.0
BUN	7.9	1.8	6.2	1.7	7.8	2.9
Creatinine	103.8	20.9	87.4[a]	19.4	96.3	27.4
ALT	68.6	48.9	65.7	40.2	54.4[a]	24.2
SAP	73.9	44.1	57.3[a]	31.6	49.8[a]	29.6
Group PreSx						
PCV	36.9	6.1	37.0	5.2	35.1[a]	4.4
TP	66.8	4.4	66.8	5.0	70.3[a]	6.0
BUN	8.8	2.0	6.9[a]	1.7	9.3[a]	3.1
Creatinine	99.5	26.4	92.3[a]	24.2	100.4	27.5
ALT	69.7	18.6	65.6	19.9	59.4[a]	7.4
SAP	66.8	38.6	66.9	26.1	55.8[a]	23.4
Group ExTub						
PCV	41.5	5.6	37.2	4.9	36.5[a]	5.4
TP	72.3	6.7	72.3	5.9	73.3[a]	6.6
BUN	7.4	1.8	5.9[a]	1.7	6.6	1.7
Creatinine	103.3	20.9	83.0[a]	19.4	93.8[a]	18.9
ALT	62.9	48.9	61.4	40.2	52.9[a]	21.8
SAP	65.3	44.1	48.4[a]	31.2	42.4[a]	22.0

s — Standard deviation.
PCV — Packed cell volume (reference range: 25% to 44%).
TP — Total protein (reference range: 55 to 76 g/L).
BUN — Blood urea nitrogen (reference range: 5.0 to 13.9 mmol/L).
Creatinine — reference range: 79 to 133 μmol/L.
ALT — Alanine transaminase (reference range: 0 to 195 U/L).
SAP — Serum alkaline phosphatase (reference range: 40 to 195 U/L).
[a] Statistically significant when compared to Day 0.

published recommendations for the prevention of neuropathic pain and provides evidence for the dosing protocol used in the current study (27). Based on the fact that onychectomy is considered an orthopedic procedure of medium to severe pain, it is likely that these findings can be extrapolated to other orthopedic surgical procedures of similar pain severity classification (39).

The clinical value of preemptive analgesia has been the subject of much debate in both human and veterinary medicine. While there are a number of published works in the human literature, there is little in the veterinary literature; however, there are at least 2 studies that demonstrate a postoperative benefit to preemptive analgesia with meloxicam (40–45). As such, this remains predominantly an opinion-based debate in veterinary medicine and is reflected by the different opinions as to the risks versus benefits. The results of this study support those of earlier publications demonstrating a benefit to preemptive meloxicam use that extended into the postoperative period (17,45); lack of benefit in other earlier studies was likely limited by their short study duration (< 24 h). Also of clinical relevance was that the study herein did not demonstrate any difference in safety assessment between preemptive or postoperative use. These findings support the benefits over risk of preemptive meloxicam use and should encourage veterinarians to make more consistent use of preemptive analgesia, especially when used in conjunction with multi-modal analgesic protocols and good supportive patient care. These findings also provide objective data to support published practice standard recommendations that embody the concept of preemptive analgesia and the treatment of predictable pain (27,37). The result also supports the evolution of preemptive to preventative pain management, whereby an analgesic protocol is not only used prior to but also for an appropriate length of time after the painful event (44). This may be of particular relevance to onychectomy in cats, as at least 1 study has demonstrated residual reductions in limb function up to 12 d postoperatively (46).

While meloxicam was shown to be an effective analgesic in this study, there was no difference in analgesia efficacy assessment between the 3- and 5-day treatment groups. This may be a reflection of factors such as small sample size, use of a multi-modal analgesic regimen, the skill level of the surgeon performing the onychectomy and sterilization procedure, and meloxicam's pharmacokinetic profile. The multi-modal analgesic protocol employed in this study made use of a potent opioid, local anesthetic blocks, and ketamine as an induction agent. Opioids are the foundation for treating acute pain and the benefits of local anesthesia and ketamine, an NMDA (N-methyl D-aspartate) receptor antagonist, are well-accepted as effective agents in mitigating central sensitization and wind-up, known as predisposing factors to heightened postoperative pain perception and the development of pathological pain (40). Additionally, based on meloxicam's 24-hour half-life, cats within the 3-day treatment group would still have had residual serum meloxicam concentrations equating to approximately 25% of the 5-day treatment group. Meloxicam dosing protocols that have employed lowest effective dosing techniques have been shown to be effective in the treatment of chronic pain, a 0.025 mg/kg dose has been demonstrated to provide some analgesic efficacy, and NSAIDs are known to have biological activity that extends beyond their serum concentration (14,21,25). This latter point is particularly relevant for meloxicam because as a highly protein-bound, acidic NSAID, it has been shown to exhibit preferential accumulation and persistence at sites of inflammation (47–49). As such, a longer study duration may have ultimately shown a difference between groups. Regardless, the lack of difference between groups also applied to the safety assessment result and, as such, it should provide the veterinarian comfort in choosing a 5-day versus a 3-day treatment regimen should the individual case indicate a benefit.

One cat had a greater than 1.5 times change in serum creatinine between days 1 and 5. While an outlier, this cat was unusual in that its pre-treatment creatinine was less than the reference range (79 to 133 μmol/L) and its 1.5× rise was still well within the lower half of the reference range. The BUN remained consistent and the cat did well clinically; this cat's changes were considered clinically insignificant.

This study had several potential limitations including small sample size, single-blinding, and lack of a placebo group. However, it could be argued that findings of statistical

significance in a small sample size are likely to have greater clinical relevance. While double-blinded studies are generally considered to be superior to single-blinded ones, the potential bias of knowing the treatment group a patient is in can be mitigated by study design whereby blinding is rigidly maintained for the individual assessing pain and the individual administering the medication is not involved in patient evaluation. That was the case in this study. Placebo-controlled studies are also considered superior to positive controlled studies; however, this study design has already been used to demonstrate the efficacy of meloxicam in a similar surgical model and is not considered ethical. Despite this, the study design did have a rescue analgesia provision; however, it was not invoked for any of the patients and further supports the efficacy of the protocol used.

The results of this study demonstrate that meloxicam, used at 0.2 mg/kg BW subcutaneously in the perioperative period followed by 0.05 mg/kg BW per day for 3 to 5 days as part of a multi-modal analgesic/anesthetic regimen employing best practices for patient support and monitoring, was an effective and safe analgesic/anti-inflammatory agent in the cat undergoing onychectomy and sterilization. The improved outcomes for gait/lameness evaluation in patients in which meloxicam was used preoperatively support the concept of preemptive analgesia. While the efficacy in this group of patients was no different between treatment groups, the demonstrated safety profile indicates that a 5-day treatment course would be well-tolerated if the individual case warrants its use in this manner.

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Appendix I. Analgesia scoring system

1 — No pain. Relaxed, freely moving. Does not resent surgical site palpation. Normal attention to environment. Playfully interactive.
2 — Faintly painful. Barely noticeable alteration from normal. May have slightly abnormal stance or gait. Orients to palpation site, but does not resent it. Observant, but restricted interaction. May sit with one paw raised, but stands on all paws.
3 — Mildly painful. Slightly restricted movement. Holds one paw raised. May stand slightly arched or tucked, with toes just touching ground. Orients and withdraws from palpation site. Licks paws.
4 — Moderately painful. Noticeably arched, abnormal posture. Non-weight bearing. Tries to escape palpation. May bite. Marked guarding. May chew, bite or shake foot. May cry, growl. Limited interest in surroundings. Will move around, but may be restless.

Appendix II. Gait/lameness scoring system
To perform assessment the cat will be gently placed in standing position (on all four limbs) and observed for 30 to 45 seconds.

Score	Criteria
1	Sound
2	Barely noticeable. May shift weight. Not lame if running
3	Noticeable, but weight bearing. Places foot down when standing
4	Bears weight occasionally, especially if needed for balance
5	Non-weight bearing

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